University of Alberta

Critically Ill Patients in Acute Renal Failure on Intermittent Hemodialysis: Predicting Episodes of Hypotension by Continuous Blood Volume Monitoring

by

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Abstract

Intermittent hemodialysis (IHD) is the standard therapy for acute renal failure which develops in 23% of all critically ill patients. During IHD hypotension occurs in 25% to 50% of patients. Blood volume monitoring has been used to prevent hypotension in the chronic renal failure population but has not been investigated in acute renal failure (ARF). This prospective observational study examined the relationship of blood volume (BV) and BV slopes to hypotension in 11 critically ill adults. The incidence of hypotension according to mean arterial pressure <70 mmHg was 70%, and according to systolic blood pressure <90 mmHg was 34%. Monitoring BV was not shown to predict hypotension in this cohort dialyzed via central venous catheters. Further study is needed to determine if different BV monitoring techniques could be used to predict hypotension.

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CHAPTER ONE

Introduction

Acute renal failure (ARF) is defined as the rapid deterioration of renal function with a subsequent buildup of nitrogenous waste products such as urea and creatinine in the body that is not due to pre-renal or post renal factors (Lameire & Vanholder, 2000). The pathophysiological abnormalities seen in ARF include changes in intrarenal hemodynamics and ischemic and toxic injury to tubular cells (Lameire & Vanholder). One of the causes of ARF is acute tubular necrosis (ATN) with pathology that involves the renal tubules and adjacent renal parenchyma (Lameire & Vanholder). ATN can be precipitated either by nephrotoxic or ischemic insults to the renal parenchyma (Lameire & Vanholder). Critically ill patients are at high risk of developing ATN secondary to their presenting problem of shock, trauma, or vascular disease (Metha, 1994; Lemeire & Vanholder). Lameire, Biesen, Vanholder, and Colardijn (1998) indicated that 23% of critically ill patients develop ARF. In comparison to other similar critically ill patients, the patient that develops ARF has a 35-50% increase in mortality (Lameire et al., 1998). Similarly, Mehta (1994) found that in ARF caused by nephrotoxins, the mortality rate is 30%, which soars to 80% when the cause is multi-system organ failure (MSOF).

The management of critically ill patients in ARF presents many problems. Mehta (1994) stated that most critically ill patients are in a hypercatabolic state producing upwards of 2 grams/kilogram (g/kg) of protein catabolic wastes, which lead to higher urea levels. This hypercatabolic state increases the risk of developing hyperkalemia and metabolic acidosis (Lameire et al., 1998). Conger (1998) suggested that these two conditions are indicators for initiation of renal replacement therapy. Furthermore, in the

critically ill patient with ARF another problem is fluid overload. Most critically ill patients require up to 4 liters /day (l/day) to meet fluid, nutritional, and drug administration requirements (Lameire et al.).

One traditional treatment modality for ARF in the critically ill patient has been intermittent hemodialysis (IHD) (Conger, 1998). However, a major complication of IHD in both the critically ill and chronic dialysis patient is hypotension. Hypotension occurs in approximately 50% of critically ill patients with ARF on IHD (Metha, 1994). Lameire et al. (1998) described hemodynamic instability seen with IHD as being caused by the massive solute removal that occurs when the patient is placed on dialysis. This movement of solutes contributes to a rapid decline in plasma osmolality that promotes the movement of intravascular water into the interstitium causing a relative hypovolemia. This osmolar inbalance is known as disequilibrium syndrome (Lameire et al.). A second factor that contributes to hypotension is a disturbance of the capillary membrane, often seen in MSOF. This disturbance increases the permeability of the capillary membrane, which then causes leakage of fluid from the intravascular space into the interstitium (Lameire et al., 1998). Even though critically ill patients may be fluid overloaded, the intravascular space can be normovolemic or hypovolemic. When placed on IHD the removal of fluid from the intravascular space can rapidly lead to decreased intravascular volume (Lameire et al.). This decrease in intravascular volume results in hypotension, which usually requires treatment with fluid, vasopressors, or the IHD may have to be aborted due to patient instability. A third factor believed to be involved in dialysis induced hypotension is failure of the cardiovascular compensatory mechanisms. There is a failure of the microvascular resistance vessels to clamp down in response to declining vascular volume

instability and hypotension ensues (Santora, Mancini, Paolini, Cavicchioli, Bosetto, & Zucchelli, 1998). The warm temperature of the dialysis bath causes peripheral vasodilation, which then leads to episodes of hypotension (Maggiore et al., 1982).

Although osmolar imbalance, inappropriate neurohumoral responses, and changes in body temperature due to the temperature of dialysis bath all appear to contribute to dialysis induced hypotension, hypovolemia is likely the common trigger or the end result of these abnormalities (Steuer, Leypoldt, Cheung, Harris, & Conis, 1994). When the fluid removal rate is more rapid than the body's plasma refilling rate, intravascular blood volume decreases. Such a rapid decrease in blood volume (BV) does not allow adequate time for the body's compensatory mechanisms to support the blood pressure and hypotension ensues (Steuer, Harris, & Conis, 1993). During IHD the intravascular compartment is exposed to two opposite forces; ultrafiltration (UF) and interstitial refill. The ratio between the established UF rate and interstitial refill capacity sets the pace of BV decrease during IHD (De Vries, Donker, & De Vries, 1994). As plasma water is removed there is a progressive reduction in BV. This hemoconcentration causes a water shift from the interstitial and cellular spaces toward the vascular compartment (Santoro et al., 1998). Subsequently, Lopot, Kotyk, Blaha, and Forejt (1996) described a continuous BV monitoring technique that could be used to detect the risk of hypotension.

BV monitors are devices that depend on the fact that blood components (red cells, hemoglobin, plasma protein, and total protein) are confined to the vascular space enabling the measurement of relative blood volume. Therefore as plasma water is removed by UF, the concentration of the vascular space increases and there is a proportional decrease in circulating BV. The plasma proteins remaining in the vascular

space exert an oncotic force resulting in increased reabsorption of fluid from the interstitial space. This rate of plasma refilling is dependent on permeability of the capillary membrane (Chamney et al., 1999). Theoretically, by monitoring BV, one should be able to predict episodes of hypotension and intervene to prevent them. Studies in the chronic IHD population have shown an ability to consistently predict the timing of hypotensive episodes (Donauer, Kolbin, Bek, Krause, & Bohler, 2000; Krepel, Nette, Akcahuseyin, Weiman, & Zietse, 2000; Andrulli et al., 2002). Further, it has been noted that if BV falls below a critical level during IHD, hypotension will ensue. Kim et al. as early as 1970 described a patient specific critical BV level that triggers intradialytic morbid events such as hypotension. They found that 80% of all hypotensive episodes occurred when the patient's absolute BV was below 2800 milliliters (mls) or 50 mls/kilogram (kg) of body weight. Yet, there has been little investigation of continuous BV monitoring in critically ill patients with ARF. The ability to continuously monitor the BV and to intervene in order to avoid hypotension during IHD may allow for the provision of optimum dialysis to the critically ill patient.

Purpose of the Study

The purpose of this study was to examine BV and BV slopes in the critically ill ARF adult patient on IHD in general systems ICU (GSICU). The relationship of BV and BV slopes to dialysis induced hypotensive episodes was examined. The hypothesis was that there is a patient specific critical BV and/or a specific BV slope that indicates forthcoming hypotension. The specific research questions addressed were:

1. What is the BV slope in the critically ill ARF patient during IHD?

2. What is the frequency of hypotensive episodes in the critically ill ARF patient during IHD?
3. Is there a critical BV that is related to hypotensive episodes in the individual critically ill ARF patient on IHD?
4. Is there a specific BV slope that is related to hypotensive episodes in the critically ill ARF patient on IHD?

Definition of Terms

Hypotensive episode was defined as a SBP below 90 mmHg or a decrease of ≥ 30 mmHg and/or a MAP below 70 mmHg (Sturnio et al. 1990). Hemodynamically unstable patients who required initiation of vasopressors or titration of vasopressors to maintain a SBP ≥ 90 mmHg were identified as having a hypotensive episode. The blood pressure (BP) had to return to normal for greater than 5 minutes to be considered a hypotensive episode. BP and/or MAP was measured by an arterial line or a BP cuff and documented on the patient's hemodialysis log (Appendix B).

Blood volume (BV) of adults comprises about 7 percent of body weight or 5 liters. Sixty percent of BV is plasma and 40 percent is red blood cells (RBC). HCT is the fraction of the blood volume composed of RBC. The plasma is comprised of proteins and cations such as sodium, potassium, calcium and the anions, chloride, phosphate and bicarbonate (Guyton & Hall, 2000). BV was monitored continuously by an optical reflection method on the Integra dialysis machine (Hemoscanning). BV was obtained at 15 minute intervals, and prior to hypotension, for each dialysis session. BV monitoring devices depend on the fact

that the blood components are confined to the vascular space enabling the measurement of relative blood volume. Therefore as plasma water was removed by UF the concentration of the blood compartment increased (HCT) and there was a proportional decrease in circulating BV (Chamney et al., 1999).

BV slopes are tracing of BV over time during the IHD session. BV slopes were obtained from a graph generated by continuous BV monitoring on the Integra dialysis machine. The BV slopes can be Flat, Linear Decrease, Concave Upward Increase and Concave Downward Decrease (Andrulli et al., 2002). The BV slope for each IHD session was classified independently by two raters.

Critical BV is defined as the decrease of BV below a specific value whereby hypotension occurs. To obtain the critical BV, the BV at each hypotensive episode during the 3 dialysis sessions was averaged to obtain the critical BV for that patient (Begin et al., 2002).

Significance of the Study

The significance of this study was to determine if a critical and/or BV slope is related to hypotensive events in the critically ill patient in ARF on IHD. If this relationship exists, monitoring BV and BV slopes could possibly prevent development of hypotensive episodes in the critically ill ARF patient.

CHAPTER TWO

Literature Review

The following databases were accessed: CINAHL, Cochrane Library, DARE, ERIC, Medline, MD Consult and PubMed between 1965 to 2005. Key words utilized for this literature search were acute renal failure (ARF), chronic renal failure (CRF), critically ill, intermittent hemodialysis dialysis (IHD), hemoscanning, hemoscan, blood volume monitoring, renal dialysis, and continuous renal replacement therapy (CRRT).

Dialysis Induced Hypotension

Paganini, Moreno, Kozlowski, and Sakai (1996) described intermittent hemodialysis as both the removal of solutes, such as urea and sodium, and the removal of fluid, that is known as ultrafiltration (UF). In IHD the removal of solutes and fluid creates an unequal osmolality between the intravascular, extracellular, and intracellular compartments. Kouw, deVries, and Oe (1989) stated that a decreased plasma osmolality means there are less solutes within the intravascular space. Following the principle of osmosis, fluid shifts into compartments that have more solutes in order to maintain homeostasis; i.e., intracellular. Fluid moving into the intracellular space creates a shift of fluid from the extracellular and intracellular compartments. Once fluid moves from the extracellular to the intracellular space, the fluid becomes unavailable for removal by dialysis (Kouw et al.). Thus, the removal of solutes from the intravascular space results in a decrease in plasma osmolality, which leads to fluid shifting intracellularily. This, combined with fluid removal via UF, can lead to an overall decrease in blood volume within the intravascular compartment. DeVries et al. (1991) found that when there was a

decrease in blood volume equal to 20% or more, patients with chronic renal failure were predisposed to the development of hypotension.

Consequently, one of the major complications of hemodialysis is hypotension, which occurs in both the chronic and acute renal failure populations (Metha, 1994; Donauer, Kolblin, Bek, Krause, & Bohler, 2000). Hypotension occurs in approximately 25 to 50% of critically ill patients on dialysis (Metha, 1994; Begin, Deziel, & Madore, 2002). Hypotension is defined as a decrease in systolic blood pressure (SBP) by 30 mmHg or SBP below 90 mmHg (Sturniolo et al., 1990) and can occur with all types of hemodialysis procedures. The occurrence of dialysis induced hypotension maybe multifactorial. Changes in plasma osmolality, autonomic neuropathy, and losses of vasoactive substances such as catecholamines are associated with dialysis induced hypotension. The amount of fluid and the rate at which it is removed (known as the UF rate) is a major factor in dialysis induced hypotension. The inability of the body to equal ultrafiltration removal with fluid obtained by plasma refill leads to decreased intravascular volume causing hypotension (Sturniolo et al.).

Kouw et al. (1989) stated that in an effort to maintain adequate SBP, the body compensates by refilling the intravascular compartment from the overhydrated interstitium, thereby counteracting the depletion of BV. Kouw et al. also stated that although refilling is not completely understood, a rise in oncotic pressure caused by hemoconcentration is believed to be the major driving force for refilling. Several other forces, such as changes in tissue hydrostatic pressure, and tone of capillary sphincters may contribute to plasma refilling. Refilling occurs from the interstitium, a pool of

extracellular fluid that can be mobilized when a decrease in blood volume has occurred (Kouw et al.).

Kouw et al. (1989) studied the effects of the UF rate on BV, plasma refill, blood pressure, and extracellular and intracellular fluid volumes during IHD. The sample consisted of stable CRF patients (n = 6) on maintenance IHD. Three female and three male patients, aged 37 to 57 years, were dialyzed for five hours twice a week, and followed for 16 dialysis sessions. An artificial dialysis kidney, with blood flow rates of 250 milliliter /minute (ml/min) and dialysate flows of 500 ml/min were set for each session. The dialysate bath contained 141 millimoles/liter (mmol/l) of sodium with an osmolality of 284 mmol/l. Absolute blood volume was calculated based on 6.7% of predialysis weights for males and 6.2% for females. The UF rate was kept constant and the UF was read from the Gambro UF monitor. Plasma refilling was calculated as the difference between total UF volume and absolute decreased blood volume (dBV). A pre and post dialysis serum erythrocyte count, protein, sodium, and hematocrit (HCT) were collected, and SBP was measured by sphygmomanometer and recorded every hour. In some patients, intracellular and extracellular fluid was measured using the four circular electrode conductivity method; calculation of intracellular fluid and extracellular fluid was completed with an instrument only identified as the CSM 08.

Kouw et al. (1989) found that a small to moderate decrease in blood volume was well tolerated, as the resultant hypovolemia was associated with a vasoconstrictory response that preserved the SBP ($r=-0.69$, $p<0.005$). They indicated that a small (<0.1ml/min/kilogram (kg)) to moderate (0.4 ml/min/kg) loss of blood volume is almost completely compensated for by plasma refilling at low UF rates ($r=0.99$, $p<0.005$). Kouw

et al. also found that plasma refilling does increase at higher UF rates; however, as the gap between refilling and loss widens there is a severe decrease in blood volume, which caused hypotension. By measuring conductivity, the direction of transcellular fluid shift was determined. Kouw et al. found that UF did not influence transcellular fluid shifts that were from extracellular to intracellular compartments. They also discovered that fluid shifted from extracellular to intracellular spaces with small decreases in blood volume but changed direction to intracellular to extracellular spaces when blood volume decreases were large. They hypothesized that fluid shifted from extracellular to intracellular compartments due to a higher osmotic gradient.

Blood Volume Monitoring to Predict Hypotension

When fluid removal is more rapid that the body's plasma-refilling rate there is a fall in intravascular volume. This imbalance is considered to be one of the major factors causing dialysis-induced hypotension (Steuer, Harris, & Conis, 1993). Steuer et al. examined an optical measurement tool for monitoring blood volume to determine its accuracy, and also studied whether BV status could be used to alter UF rates to prevent hypotensive events during IHD. The optical measurement tool was an automated instrument that through a photometric technique graphically displayed the trend of HCT as well as the percentage of BV change during the dialysis treatment. Their sample consisted of patients (n=4) who were followed for 15 dialysis treatments. Continuous trends of HCT and BV percentages were logged every 15 minutes over the treatment period.

Steuer et al. (1993) compared laboratory blood samples of HCT to the dialysis machine measured BV. The data indicated that BV monitoring by the dialysis machine

was accurate (r=0.996) with a standard deviation of 1.16 when compared to laboratory samples of HCT. Data also suggested a correlation between percentage BV change and systolic blood pressure (SBP). Steuer et al. (1993) discovered that significant drops in SBP were preceded by rapid or prolonged decreases in BV, whereas minimal decreases in BV (< 10%) were not associated with changes in SBP. Findings further indicated that there may be a threshold or target HCT value at which hypotension occurs for individual patients. Steuer et al. concluded that the optical method did accurately measure HCT and percentage of BV change, and stated that altering UF rates to equilibrate the rate of vascular volume depletion to plasma refilling rate could reduce hypotension.

DeVries et al. (1993) also evaluated the accuracy of optical measurement of BV, and examined the relationship of hydration status to BV changes and episodes of hypotension. The principle of the optical reflection method is based on the reflection of infrared light by the erythrocyte membranes. The amount of reflected infrared light is directly proportional to the erythrocyte concentration and it provides information about changes in the amount of circulating BV continuously. The sample consisted of patients (n=37) who were divided into three groups: dehydrated, normohydrated, or overhydrated. All patients received four hours of dialysis three times a week. The UF rate and dialysate concentration remained constant throughout the entire treatment. They measured SBP and heart rate (HR) every 30 minutes. To determine plasma refill, the extracellular fluid volume (EFV) was assessed by means of conductivity measurement by four circumferential electrodes on the lower limbs and continuous BV was monitored by optical reflection method on the dialysis machine. By measuring the conductivity of the EFV they were able to determine post dialysis EFV which was the basis for the division

of patients into the three groups. Low post dialysis EFV was indicative of interstitial dehydration whereas high post dialysis EFV indicated overhydration.

DeVries et al. (1993) found that the post dialytic EFV of the three groups differed. To assess the relationship of post dialytic EFV to hydration status the percentage of IHD sessions in which hypotension occurred was calculated for each patient. The highest percentage (48%) of hypotensive episodes occurred in the dehydrated group ($p<0.001$). Decreases in BV and SBP were greatest in the dehydrated group (percentage of hypotension: 48.5% +/- 20.2%). In seven out of 20 IHD sessions in which patients experienced hypotension, the BV decrease during these dialysis sessions was significantly higher at 5 minutes (6.69% +/-3), 10 minutes (6.81% +/-4), and 15 minutes (7.00% +/-5) preceding hypotension ($p< 0.005$). DeVries et al. concluded that continuous measurement of changes in BV by means of optical reflection method could be used to detect hypovolemia.

DeVries, Donker, and DeVries (1994) evaluated the clinical value of continuous monitoring of BV during IHD by means of the optical reflection method, and tested the predictive value of the optical method to occurrence of hypovolemia induced episodes in CRF patients (n=23). They also evaluated the graphs produced by continuous BV monitoring for a pattern that might indicate approaching hypotension. During the IHD sessions, BV was measured continuously, while BP and HR were recorded every 30 minutes or when a hypotensive episode occurred. The IHD sessions were divided into two groups: sessions with hypotension and sessions without hypotension. In nine of the 23 sessions, hypotension occurred when the mean arterial pressures (MAP) were 64+/-12 mmHg compared to sessions without hypotension in which the MAP were 93+/-18

mmHg. DeVries et al. then evaluated the BV graph, which showed a 3 phasic pattern that could be divided into slope 1, slope 2, and slope 3. No difference was found between slope 1 in the hypotensive and non-hypotensive group. They suggested that slope 1 represented fluid refill from the overexpanded intravascular compartment. They discovered that slope 2 started earlier and lasted one hour longer in the non-hypotensive group than in the hypotensive group. Slope 2 indicated the withdrawal of UF fluid that is fully compensated for by interstitial refill. Slope 3 which was steeper than slope 1 and slope 2 was more frequent in the hypotensive group compared to the non-hypotensive group ($p<0.025$). Slope 3 indicated an underexpanded intravascular compartment that is only partially compensated for by interstitial refill. DeVries et al. concluded that the optical reflection method of continuous BV monitoring made it possible to gain a clear insight into the changes in intravascular volume during IHD. The shape of the BV slope could be a predictor of hypotension during IHD. For example, as a patient's BV slope approaches the shape of slope 3, they are more likely to experience hypotension due to inadequate plasma refill from the interstitium (DeVries et al.).

Steuer, Leypoldt, Cheung, Harris, and Conis (1994) studied the relationship between dialysis induced volume depletion and intradialytic morbid events (IME). IME were defined as hypotension (MAP < 70 mmHg), and cramping or lightheadedness that led to dialysis staff intervention. Sample consisted of stable (n=8) and hypotensive prone patients (n=8) in a chronic dialysis unit. Each patient was studied on six separate occasions for a total of 93 IHD sessions. The UF rate was kept constant, BP and HR were measured every 15 minutes, and BV was monitored continuously. Steuer et al. discovered that IME occurred in 52% of the IHD sessions. In those sessions with IME, UF rates were

higher ($p<0.001$); however, changes in BV were no different between sessions with or without IME. SBP decreased during IHD and this decrease in SBP was related to decreases in BV. BV decreased more (–18.1+/-1.76%) in sessions with IME compared to sessions without IME (–14.5+/-6.7%) ($p<0.001$). Steuer et al. determined that there was a difference in the percentage of BV decrease required to cause hypotension between patients. The rate of BV change was lower (5.6%) in sessions with no IME than in sessions with IME (12.2%) ($p<0.001$). Thus, it was demonstrated that MAP decreases with decreasing BV and increasing HCT ($p<0.05$), and in many patients on IHD, this high rate of BV change may indicate that IME are forthcoming. Further, the data indicated that IME occurred at a patient specific HCT threshold. IME did not occur when this HCT threshold level was not exceeded (mean standard deviation of observed HCT threshold was 1.4). The data supports the hypothesis that a critical BV exists for individual patients and can be determined by continuous monitoring of HCT or BV (Steuer et al.).

Leypoldt, Cheung, Steuer, Harris, and Conis (1995) sampled CRF patients (n=16) during six IHD sessions for a total of 93 sessions. The UF rate was constant; HCT was measured every 15 minutes by laboratory and by continuous BV monitoring. In this study HCT was determined by optical reflection method which correlated well with those determined by centrifugation ($r=0.89$). The authors calculated circulating BV levels by determining the rate of change of HCT shortly before and after UF was stopped, in patients who experienced IME such as hypotension, cramping, or lightheadedness. They determined that discrepancies between HCT estimates were larger between different treatment sessions than within the same session ($p<0.001$). This study did not confirm

that BV decreased more rapidly at the beginning of the session, as was suggested by other studies. Lepoldt et al. suggested that this variation was due to the hydration status of tissues and physiological compensatory responses affecting the heart. The relative change in BV was found to correlate with the amount of fluid removed during IHD, and IME occurred when the HCT reached a patient specific threshold. This implied that IME occurs when the absolute circulating BV decreases to a critical value.

Critical Blood Volume Threshold versus Blood Volume Curves

Steuer, Leypoldt, Cheung, Harris, and Conis (1994) evaluated whether decreases in BV with decreasing MAP and rising HCT were related to intravascular volume depletion and IME during IHD. The sample was selected by staff as either stable CRF patients (n=8) or hypotensive prone CRF patients (n=8) based on previous clinical knowledge of the patients. They monitored BV continuously and sampled HCT every hour as both are inversely related to blood volume changes. The authors discovered that the rate of BV change in IHD sessions without hypotension was lower (5.6%/hr +/- 3.6) than sessions with hypotension (12.2%/hr +/-5.5) ($p<0.001$). Twelve out of 16 subjects exhibited IME when HCT reached a patient specific critical BV threshold. Steuer et al. confirmed that blood pressure declined during IHD and that this decrease in SBP was related to decreases in BV and increases in HCT. Steuer et al. also found that MAP decreases with decreasing BV, and increasing HCT often indicated that IME were forthcoming ($r= -0.57$, $p<0.05$), and 80% of all hypotensive episodes occurred when the patient's absolute BV was below 2800 mls or 50 mls/kg. They concluded that the consistency of this HCT threshold before IME supported the hypothesis that a critical BV

exists for individual patients and critical BV can be determined by continuous BV monitoring.

In the first phase of a study by Steuer, Leypoldt, Cheung, Senkjean, and Conis (1996), the HCT at which hypovolemic symptoms occurred for individual subjects was identified. The low standard deviation of the HCT values (0.4 to 1.3 SD) indicated consistency of the HCT threshold (40.9+/-1.3 SD), while the large variation of this value between patients suggested that it was patient specific. The second phase of this study was designed to determine whether manipulation of intradialytic BV to avoid the HCT threshold would decrease episodes of hypotension. They enrolled CRF patients (n=6) and followed them for a combined 106 IHD sessions. As the subjects were prone to hypotension, they monitored continuous BV, HCT and MAP at 15-minute intervals. The study was conducted over a period of 4 months. With the patient specific HCT level for hypotension determined, the treatment was started with a UF rate 25% higher than the calculated UF rate prescribed on the basis of the patient's target dry weight. This rate was maintained until the patient's HCT level reached or exceeded the HCT limit. At this time the nurses decreased the UF rate by decrements of 25% to maintain the HCT below the limit. In seven of the sessions in which hypotension occurred, the HCT exceeded each individual's HCT critical threshold. Thus, Steuer et al. support previous findings that patients may develop intradialytic symptoms at a patient specific HCT threshold. They showed a two-fold improvement in patient symptoms such as hypotension, muscle cramping, or lightheadedness when the UFR was manually reduced by 25% to avoid the HCT threshold.

Howard, Palmer, Howard, Stephen, Goldberger, and Shabshab (1998) examined the effect of monitoring BV to determine if there was an impact on patient hospitalizations due to complications associated with UF removal such as fluid overload or hypotension. They sampled patients (n=113) from two chronic dialysis units. One dialysis unit used BV monitoring during IHD, the other dialysis unit did not. For the dialysis unit that monitored BV, Howard et al. found a 48% decrease in patient hospitalizations for fluid overload. There was a marked difference in the frequency of hypotension between the two units, with a higher frequency of hypotension occurring in the unit that did not monitor BV ($p<0.0005$). As well there was an increased requirement of normal saline to treat hypotension in the unit that did not monitor BV continuously ($p<0.0005$). Howard et al. found that UF could be decreased or terminated when a critical reduction in BV was reached, which minimized the likelihood of the patient developing hypotension. It was also discovered that this critical threshold of BV had to be determined for each individual patient. This critical threshold was determined by continuously monitoring BV and determining the threshold at which an IME occurred.

Although Howard et al. (1998) found that a critical threshold of BV could be determined for every patient, Donauer, Kolbin, Bek, Krause, and Bohler (2000) suggested that this level could only be found in patients who had hypovolemia type one hypotension. Donauer et al. outlined that type one hypotensive patients experienced hypotension due to hypovolemia, whereas type two hypotensive patient's hypotension was related to failure of compensatory mechanisms. Donauer et al. compared the effects of constant UF rate with five different UF profiles on IHD related side effects. They also evaluated the benefit of BV measurement for the prediction of IHD related side effects

such as hypotension. The sample consisted of patients (n=59) who underwent a combined total of 180 IHD sessions. The five UF Profiles were defined as presented in Appendix A.

Once data collection started, it immediately became evident that UF Profiles 3 to 5 had worse outcomes such as hypotension, therefore no further patients were assigned to these groups (Donauer et al., 2000). In UF Profile 0 hypotension occurred in 10.6 % compared to 5.7% in UF Profile 1. This difference in episodes of hypotension between UF Profile 0 and UF Profile 1 was not statistically significant. However, when UF Profile 0 and 1 were compared to UF Profile 2 which had a 19.4 % incidence of hypotension, this was statistically significant ($p<0.05$). Donauer et al. concluded that IHD sessions with hypotensive episodes were associated with significantly lower relative BV values when compared to asymptomatic IHD sessions. High UF rates either intermittently, or over long periods during the IHD sessions, were responsible for increased side effects. Donauer et al's, findings indicated that in clinical practice, BV measurement is unreliable for prediction of hypotensive episodes for two reasons. First it is known that the critical BV threshold is at a different level for each patient. Second their data indicated that BV monitoring was only predictive in a subgroup of hypotensive prone patients which they identified as type one. They concluded that BV monitoring to determine the critical threshold to avoid hypotension is only effective for a subset of patients with type one hypotension, as their hypotension is due to hypovolemia, and the UF rate can be adjusted to prevent hypotension.

Donauer et al.'s (2000) findings were supported by the inability of Krepel, Nette, Akcahuseyin, Weiman, and Zietse (2000) to determine a relationship between BV and UF or a critical level of reduction in BV in patients with diastolic dysfunction with

impaired cardiovascular compensatory abilities. They studied intra and interindividual variability of relative blood volume (RBV) and the correlation of RBV with SBP, HR, and inferior caval vein (IVC) diameter. The sample consisted of CRF patients (n=10) with diastolic dysfunction. IHD sessions were performed three times a week per patient and only patients requiring at least 1000 mls of UF were included. The change in RBV correlated with UF volume both at 60 minutes ($r=0.69$, $p<0.0001$) and at 240 minutes ($r= -0.63$, $p<0.0001$). Krepel et al. found no significant correlation between change in RBV and SBP or DBP at 60 minutes or 240 minutes. In patients who experienced hypotension, RBV varied markedly (co-efficient of variability ranged from 0.48 to 0.23, $p<0.001$) and the HCT ranged from 0.27 to 0.37. Krepel et al. also found that six of seven patients, during the IHD session, were bradycardiac not tachycardiac, indicating that hypotension might have been caused by failure of the CV system to respond, not hypovolemia due to UF removal. Therefore, they concluded that BV monitoring was of limited use in prevention of dialysis associated hypotension due to cardiovascular compensatory failure. Furthermore, the critical level of reduction in BV at which hypotension occurred depended on cardiovascular compensatory mechanisms much more than reduction in BV.

Since some investigators have been able to determine a critical BV threshold whereas others have not, this has lead to research on the role of BV curves in predicting hypotensive episodes. Beige et al. (2000) used computational analysis of BV curves to determine if it would be possible to predict the risk of IME during IHD. The sample consisted of unselected CRF patients (n=159) for a total of 380 IHD sessions. During the IHD sessions, BV was monitored continuously, SBP was measured every hour, and the

UF rate was constant. Data from 380 IHD sessions showed that in 21% (n=46) of the sessions IME occurred. From the analysis of the BV curves, Beige et al. defined the following parameters: long term variability, which expresses the area between the real curve and it's linear regression line representing variability over the entire BV tracking period during dialysis; and short-term variability, which represents the mean deviation of BV data points from the regression line. In all treatments, the long-term and short-term variability indices and slope of the BV curves were significantly decreased 10 minutes before an IME. The long-term variability index in sessions with IME was 6.92%+/-5.37 compared to 13.56%+/-11.57 in sessions without IME ($p<0.0007$). This index decreased to 1.55%+/-4.04 ten minutes prior to an IME. The short-term variability index in sessions with IME was 1.21%+/-0.52 versus 1.24%+/-0.83 in sessions without IME. Ten minutes prior to an IME the short-term variability index decreased to 0.53%+/-0.58. Begin et al. found that the slope of the BV curve in treatments with IME was –0.022+/-0.023 compared to –0.015+/-0.007 in sessions without IME. The slope also decreased to –0.07+/-0.09 10 minutes prior to an IME. The slope of the BV curve was increased an average of 3.5 fold. Beige et al. concluded that the slope of the BV curve indicates reduction in BV and is associated with an IME such as hypotension.

A multicenter prospective study to clarify the mechanism of symptomatic intradialytic hypotension and how to best predict such hypotensive events was conducted by Andrulli et al. (2002). The sample consisted of patients (n=123) who were placed into three groups: normotensive (group A), intradialytic hypotensive (group B), and hypertensive (group C). Curves of BV reduction were classified as Flat, Linear, Decreased, Concave Upwards Decrease, Concave Downwards Decrease, or

Indeterminate. The greatest reduction in BV occurred in the hypotensive group; however, this was not statistically significant (p=0.879). As well, group B had the greatest number of hypotensive episodes (44%, p<0.001). Of these 44 % (n=38 patients), 31% experienced hypotension when BV had decreased by a minimum of 13.9%. However, the reduction in BV was not significantly different among the three groups. Andrulli et al. concluded that BV monitoring during IHD could not predict whether a patient would be hypotensive and the possibility of predicting a critical BV level at which intervention could prevent hypotension was not possible. This could be due to the fact that the hypotensive prone group B was comprised of older patients with associated comorbities such as diabetes and left ventricular hypertrophy which could impair the ability of their cardiovascular system to compensate. However, Andrulli et al. found that the frequency distribution of the BV curves was statistically significant among the three groups (p<0.001). The hypotensive group had a greater frequency of the Concave Upwards Decrease BV profile suggesting a possible role of a large BV reduction in the first minutes of dialysis in the genesis of hypotension. Andrulli et al. indicated that the different distribution of BV curves maybe caused by different plasma refill timing, which maybe delayed in hypotensive prone patients. Thus, they concluded that there maybe a role for monitoring BV curves in predicting hypotensive events.

The aim of a study by Mitra, Chamney, Greenwood, and Farrington (2002) was to define parameters that might characterize BV changes during UF at varying states of hydration and to assess whether using such parameters could predict hemodynamically instability during UF. The parameters that they analyzed were BV, magnitude of BV change during UF, volume of UF pulse in milliliters, magnitude of BV change during

refill, initial refill rate, UF linear divergence, mean values for UF, and critical volume threshold. Patients (n=30) underwent online BV monitoring during an IHD session with intermittent UF pulses until onset of hypotension. The initial 40-minute UF pulse removed 40% of the interdialytic weight gain followed by three additional 40-minute UF pulses of 20%, between each pulse there was a 20-minute UF free period. The occurrence of hypotension was not different at a BV less than 90% or greater than 90 % ($r=0.40$, $p<0.01$). Hypotension was statistically more common in patients with a BV less than 90% of the baseline value ($p=0.001$) at the start of UF removal. The parameter that best correlated with episodes of forthcoming hypotension was linear divergence ($r=0.817$, $p<0.001$). When the patient approached dry weight, the BV decline during UF switched from exponential to linear decay, which indicated failing vascular refill. All patients with a mean value of UF greater than 22 and 93% of patients with linear divergences less than 85% developed hypotension during a UF pulse. Mitra et al. concluded that the incidence of hypotension was similar whether BV was less than or greater than 90% of the baseline value. Mitra et al. concluded that patterns such as linear decay as seen by BV slope monitoring maybe more powerful predictors of approaching dryness or impending vascular instability than BV monitoring.

With the role of BV monitoring established in predicting hypotensive episodes in CRF. Research is now focusing on the use of positive feedback mechanisms in hemodialysis machines that adjust UF removal based on BV monitoring. BV is monitored and the UF removal is adjusted to avoid hypotension.

Blood Volume Regulation

Begin, Deziel, and Madore (2002) did a prospective crossover trial to determine whether BV regulation improved the number of hypotensive-related events in the chronic IHD population. The sample included seven patients for a total of 12 IHD sessions. The effect of the BV regulation system was studied in an "ab ab ab" crossover design alternating six consecutive dialysis sessions with BV regulation (a), with six consecutive standard dialysis sessions (b), for a total of 36 sessions per patient. Each "ab" period consisted of 4 weeks for a total period of 12 weeks. Data demonstrated significant improvement in number of event free IHD sessions with BV regulation compared to standard dialysis (50.8% vs. 29.2, $p<0.01$). BV regulation was associated with a 74% increase in the frequency of event free dialysis sessions in hypotensive prone patients ($p<0.001$). There was also a progressive increase in percentage of event free sessions from period 1 to period 3, increasing from 33.3% in period 1 to 57.1% in period 2 and 63.9% during period 3. The percentage of event free sessions was better with BV regulation compared with standard dialysis for all time periods ($p<0.05$). The authors concluded that BV regulation decreased the incidence of hypotension during dialysis in their study participants.

The aim of a four month prospective, multi-center, crossover, parallel group study by Santoro et al. (2002) was to compare BV regulation system against standard IHD to determine if there is a decrease in hypotensive episodes in hypotensive prone patients. In the IHD sessions using BV regulation, the UF rate was automatically corrected to avoid the patient specific HCT threshold, and in standard IHD the UF rate was constant regardless of the HCT level. They also sought to identify patient parameters that would

identify patients who would benefit most from continuous and automatic BV control. The sample consisted of hypotensive prone patients (n=35) from 10 CRF dialysis units. The patients also had to present with one of the following comorbidities for inclusion: cardiac disease, diabetes, or hypertension. Patients were randomized into one of either treatment sequences ABAB or BABA. The A period of the sequence consisted of standard IHD with BV and MAP monitoring with UF rate constant throughout the session; the B period of the sequence was comprised of BV regulation that corrected the UF rate to avoid a patient specific critical HCT level. There was a 30% decrease in IME in BV regulated sessions compared to standard sessions ($p<004$). Patients who had fewer hypotensive events during standard IHD did not benefit from the addition of BV regulation systems. BV regulation systems proved to be the most beneficial in CRF patients who were more critical, defined as patients with hypotensive frequency higher than 20% during IHD. Santora et al found that the greater cardiovascular instability during dialysis, the greater the benefit the patient derived from BV regulation ($p<0.001$). Also, there were hypovolemic variations in BV, both at the end of the session and at the moment when hypotension occurred in the more critical patients. BV variation was higher in the more critical CRF patients in comparison to the stable patients, with a difference of more that 3% ($p=0.08$). Santoro et al. concluded that BV regulation was more effective in preventing hypotension during dialysis with patients who had refilling problems and intradialytic hypovolemia.

Thus, support for monitoring of BV slopes in predicting forthcoming IME in CRF with hypotension is growing. However there are few studies in the critically ill patient with ARF. A prospective observational study conducted by Tonelli, Astephen, Andreou,

Beed, Lundrigan, and Jindal (2002) assessed if online BV monitoring could predict hypotension in critically ill patients (n=20) with ARF in the Intensive Care Unit (ICU) for a total of 57 dialysis sessions. All treatments were completed with a biocompatible filter, constant UF and dialysate conductivity. BP, HR, and BV were measured every 10 minutes. Tonelli et al. did not demonstrate a critical BV threshold at which hypotension occurred in the critically ill patient with ARF. They also found no relationship between BV, BV slopes, and blood pressure. Tonelli et al. concluded that continuous BV monitoring did not decrease the incidence of hypotension or increase the ability to predict hypotension in the critically ill patient dialyzed through central venous catheters. Tonelli et al. hypothesized that the failure to demonstrate the relationship between BV, BV slopes, and BP maybe due to the large number of IHD sessions that were performed through a subclavian or internal jugular catheter. Most of plasma refilling occurs from the peripheral extracellular compartments (i.e., legs) with minimal contribution occurring from central extracellular and intracellular compartments. Therefore the correlation between BV and BP might differ when dialysis catheters are placed in the femoral rather than the subclavian or internal jugular veins.

Summary

Research to date supports the benefit of continuous BV monitoring in the chronic renal failure patient (Steuer, Harris, & Conis, 1993; DeVries et al., 1993; DeVries, Donker, & DeVries, 1993), especially in the hypotensive prone patient (Steuer, Leypoldt, Cheung, Harris, & Conis, 1994; Donauer, Kolbin, Bek, Krause, & Bohler, 2000). Donauer et al's. findings also indicated that BV monitoring was only effective in predicting hypotension in patients with hypovolemic hypotension (Type 1) and not with

patients with hypotension caused by cardiovascular dysfunction (Type 2). Recent research indicates that the patient's critical BV threshold must be determined for the patient to benefit from BV monitoring in the prevention of dialysis induced hypotension. However, the use of BV monitoring has not been studied as intensely in the critically ill patient with ARF requiring IHD. Critically ill patients with ARF are frequently catabolic, hemodynamically unstable, and often have substantial fluid volume excess (Paganini et al., 1996). In addition to their underlying disease they frequently have compromised cardiovascular compensatory mechanisms (Paganini et al.). These patients require efficient and carefully planned hemodialysis to provide optimal renal support (Conger, 1998). The need for stable dialysis in the critically ill patient with ARF has been emphasized as dialysis induced hypotension maybe responsible for prolongation of ARF by potentially re-insulting the kidneys (Conger, 1998). Tonelli, Astephen, Andreou, Beed, Lundrigan, and Jindal (2002) did not show any ability to predict hypotensive episodes in critically ill patient in ARF on IHD. The Intensive Care Unit where their study took place did only IHD, so there may have been a larger portion of critically ill patients with Type 2 hypotension versus Type 1 hypotension. In many Intensive Care Units that use continuous renal replacement therapy (CRRT), the more critically ill patients with cardiovascular dysfunction would be on CRRT not IHD. IHD is then used on the more hemodynamically stable critically ill patient who may have Type 1 hypotension versus Type 2 hypotension. So the question that arises is whether continuous BV monitoring in the stable critically ill patient with ARF can predict hypotensive episodes.

CHAPTER THREE

Methods

Design

A prospective observational design (within subject repeated measures) was used to evaluate the relationship of blood volume (BV) and BV slopes to the development of hypotension in the critically ill acute renal failure (ARF) patient on intermittent hemodialysis (IHD). BV, heart rate (HR), systolic blood pressure (SBP), and mean arterial pressure (MAP) were documented by the nurse every 30 minutes on the patient's hemodialysis log (Appendix B) for 3 concurrent dialysis sessions and every 15 minutes by the dialysis machine. BV and BV slopes were downloaded from the Integra dialysis machine into an Exalis program. The length of the dialysis treatment was determined by the Intensivist based on an estimation of the amount of time required for adequate clearance of uremic toxins and safe removal of fluid in order to avoid hypotension. The UF rate and dialysate osmolality were constant throughout the dialysis session. The dialysate temperature was maintained at the current standard of 37 degrees Celsius or 1 degrees cooler than the patient's temperature. Demographic variables (age, gender, BMI, APACHE II score, diagnosis, comorbities, and previous renal dialysis treatments) and clinical variables (electrolytes, urea, creatinine, HCT, hemoglobin, temperature, and medications) were documented for each patient on the data collection sheet (Appendix C). In addition, IHD variables such as length of session, amount of fluid removed, anticoagulation, site of dialysis catheter, and treatment of hypotension were documented for each IHD session on the hemodialysis log (Appendix B).

Sample

The sample was recruited from the general systems intensive care unit (GSICU) at the Royal Alexandra Hospital. The sample is comprised of critically ill patients with ARF requiring IHD who met the following inclusion/exclusion criteria and voluntarily consented to be in the study. Inclusion criteria were:

1. 18 years of age or older.
2. diagnosed with ARF requiring IHD.
3. hemodynamically stable with ARF requiring IHD.

Exclusion criteria were:

1. less than 18 years of age.
2. on IHD for isolated hyperkalemia not caused by ARF.
3. on IHD for drug overdose.
4. on IHD with a diagnosis of chronic renal failure.
5. receiving blood transfusions during IHD.

GSICU patients who required IHD were identified each morning by the researcher. There were approximately 59 patients in GSICU who required IHD during the data collection period of August, 2004 to May 2005. A sample of 11 patients for a total of 33 IHD sessions was obtained over a 9 month data collection period.

Data Collection Protocol

Prior to initiating data collection, inservices were given to all Intensivists and Registered Nurses that perform IHD in GSICU. The inservices were conducted by the researcher and included the purpose of the study, study protocol for data collection, and programming of continuous BV monitoring. An information binder containing information about the study, including contact number of the researcher was kept in GSICU. The following data collection steps were followed for all IHD sessions:

1. The researcher determined if a patient met the inclusion/exclusion criteria of the study.
2. If inclusion/exclusion criteria was met, the researcher explained the study and obtained informed consent (Appendix D) from the patient, significant other, or family.
3. Once consent was obtained, the researcher documented the patient's demographic data from the patient's health record onto the data collection sheet (Appendix C).
4. Pre-dialysis serum urea, creatinine, hemocrit (HCT), hemoglobin (Hgb), albumin, sodium, chloride, bicarbonate, and potassium (Appendix C) was obtained at 0300 hours per unit protocol prior to each IHD treatment.
5. The Intensivists or designate indicated how they determined ultrafiltration (UF) removal by completing a flow sheet (Appendix E). It included the following indicators that could be selected; daily fluid balances, estimate of edema, chest X-ray appearance, central venous pressure (CVP), or pulmonary capillary wedge pressure (PCWP).
6. The dialysis nurse programmed the dialysis UF removal, dialysate osmolality, and length of run, as per Intensivist's orders.
7. SBP and MAP, as measured by arterial line was documented by the dialysis nurse on the hemodialysis log (Appendix B) initially, every 30 minutes thereafter, and with every episode of hypotension. As well the nurse documented HR, BV and UF rate initially, every 30 minutes thereafter and with every episode of hypotension.

8. BV monitoring and non invasive blood pressure (NIBP) monitoring was initiated by the dialysis nurse on the dialysis machine and BV, UF rate, SBP, MAP and heart was collected by the machine initially, and every 15 minutes thereafter.
9. The researcher downloaded the BV and BV slope into the exalis program for each IHD session.
10. The researcher classified the BV slope as either Flat, Linear Decrease, Concave Upward Decrease, Concave Downward Decrease or Indeterminate. Then the intensivist classified the BV slope blinded to the classification given to the BV slope by the researcher.
11. The hemodialysis log (Appendix B) was used to document IHD session prescription (UF only vs. hemodialysis), length of treatment, anticoagulation, site of dialysis catheter and treatment for hypotension during IHD.
12. Post-dialysis serum urea, creatinine, HCT, Hgb, sodium, chloride, bicarbonate, and potassium were drawn 6 hours after the IHD session as per GSICU protocol.

Data Analysis

Descriptive statistics such as mean, standard deviation, median, range and percentages were calculated for all variables. Critical BV was calculated by averaging the BV prior to each hypotensive episode during the 3 IHD sessions. Frequency of hypotensive episodes was calculated per BV slope classification. Inter-rater reliability of BV slope classification was assessed using a Kappa statistic. The relationship between BV and MAP and SBP was examined using general linear regression analysis, and Chi-square analysis was done to examine the relationship of BV slopes to frequency of hypotensive episodes.

Ethical Considerations

Ethical approval was obtained from the Health Ethics Review Board, University of Alberta. Support from the Medical Director and Nurse Manager of the GSICU was also obtained. Patients meeting the inclusion criteria were approached by the researcher and informed of the purpose of the study. Each patient who consented to participate in the research study did so voluntarily and signed a consent form (Appendix D) prior to participation. If a patient was unable to consent, family or significant other were approached regarding possible participation. The researcher indicated that there would be no consequence to the patient's care if they choose not to participate in the study, or withdrew from the study at any time.

There was no direct benefit or risk to participating in the study. The study was to observe BV, BV slopes, and episodes of hypotension. The researcher explained to the patient and/or family that IHD is the standard of care for patients in the GSICU with acute renal failure and that the only difference with being in the study was that information from the health record would be collected for analysis.

All data were kept confidential. The patient's name did not appear on any data. The data were coded with a study number and will be stored and locked in a secure location for five years. Material that will be published regarding the findings of this study will not include any patient's name.

CHAPTER FOUR

Findings

The purpose of this study was to examine the relationship of blood volume (BV) and BV slopes to hypotension in the critically ill acute renal failure (ARF) adult patient on Intermittent Hemodialysis (IHD) admitted to the Royal Alexandra Hospital (RAH) General Systems Intensive Care Unit (GSICU). Hypotensive episode was defined as a systolic blood pressure (SBP) below 90 mmHg or a decrease of $\geq$ 30 mmHg and/or a mean arterial pressure (MAP) below 70 mmHg. The blood pressure had to return to normal for greater than 5 minutes to be considered a new hypotensive episode. Hemodynamically unstable patients who required initiation of vasopressors or titration of vasopressors to maintain a SBP $\geq$ 90 mmHg were identified as having a hypotensive episode. A prospective observational design (within subject repeated measures) was used during the study period of August, 2004 to May, 2005. Vital signs and IHD variables were collected every 15 minutes for 3 IHD Runs. Critical Blood Volume (CBV) was determined for each patient by averaging the blood volume prior to episodes of hypotension for the 3 IHD Runs. Linear regression was done to determine the relationship between BV and hypotension, and Chi-square was done to examine the relationship of BV slopes to frequency of hypotensive episodes.

Description of the Sample

There were 59 patients admitted to the RAH GSICU during the data collection period who required IHD. Of these 59 patients, 44 patients did not meet inclusion criteria and 15 patients were enrolled in the study. The reasons for excluding the 44 patients were as follows: 23 had chronic renal failure (CRF), 7 were overdoses, 5 deceased, 2 were

discharged, and 7 were unable to consent to participate in the study. Analysis was completed on 11 patients, as one patient withdrew consent and 3 patients ARF resolved prior to completion of data collection. Table 1 presents the characteristics of the patients (n=11) enrolled in the study. The mean age of patients was 55.73 ± 20.6 years (range: 19-87 years), with 18.2% (n=2) greater than 70 years of age. The majority of patients (n=5) were between 51-70 years of age. Men accounted for 63.6% (n=7) of the sample. The majority of patients (n=6, 54.5%) had a BMI in the range of 20 to 30. The most frequent admitting diagnosis was respiratory failure (n=4, 36.4%), and the most frequent co-morbidity was a combination of renal insufficiency, coronary artery disease and diabetes mellitus, at 27.3% (n=3). The mean Apache II Score was 22.73 ± 6.69, with a range of 13 to 33. The most common etiology of ARF was acute tubular necrosis due to shock at 45.5% (n=5), followed by rhabdomyolysis at 27.3% (n=3). All patients received some form of hemodialysis prior to enrollment in the study, the most common form being CRRT (n=5, 45.5%).

Intermittent Hemodialysis Characteristics

The characteristics of the IHD Runs per patient are outlined in Table 2. The length of the IHD Run was determined by the Intensivist based on an estimation of the amount of time required for adequate clearance of uremic toxins and safe removal of fluid in order to avoid hypotension. The length of IHD Run ranged from 4 to 7 hours and varied between the IHD Runs. A 6 hour IHD Run was the most frequent length (36.4% in IHD Run #1, 45.5% in IHD Run #2, and 63.6% in IHD Run # 3, respectively).

Table 1
Patient Characteristics (N=11)

Characteristic	Frequency	(%)	Characteristic	Frequency	(%)
Age			**Comorbidities**		
18-30	2	(18.2)	Diabetes Mellitus	1	(9.1)
31-50	2	(18.2)	Cancer	2	(18.2)
51-70	5	(45.5)	Cancer & HTN*	1	(9.1)
71-90	2	(18.2)	Vasculitis	2	(18.2)
			Renal Insufficiency, CAD* & Diabetes Mellitus	3	(27.3)
			Psychiatric	1	(9.1)
			None	1	(9.1)
Gender			**Etiology of Renal Failure**		
Male	7	(63.6)	Rhabdomyolysis	3	(27.3)
			Acute Tubular Necrosis	5	(45.4)
Female	4	(36.3)	Vasculitis	1	(9.1)
			Acute on Chronic Renal Failure	2	(18.2)
Admission Diagnosis			**Previous Dialysis Treatment**		
Respiratory Failure	4	(36.4)	IHD*	4	(36.4)
Sepsis	2	(18.2)	CRRT*	5	(45.5)
Trauma	1	(9.1)	IHD/CRRT*	2	(18.2)
Abdominal Surgery	3	(27.3)			
Cardiac Disease	1	(9.1)			
Admission Apache II Scores			**Body Mass Index**		
1-20	4	(36.4)	20-30	6	(54.5)
21-30	5	(45.5)	31-40	3	(27.3)
> 30	2	(18.2)	41-50	2	(18.2)

* CAD = Coronary Artery Disease, HTN = Hypertension, IHD = Intermittent Hemodialysis, CRRT = Continuous Renal Replacement Therapy

All hemodialysis runs were done through a central venous catheter. The most frequent site was the subclavian vein. Anticoagulation varied between IHD runs, with 54.5% (n=6) having citrate anticoagulation in IHD Run #1, versus 45.5% (n=5) having heparin. By IHD Run #3, heparin use increased to 81.8% (n=9) and citrate decreased to 18.2% (n=2). The dialysate temperature was maintained at the current standard of 37 degrees Celsius (°C) or 1 degree cooler than the patient's temperature. The most common dialysate temperature was 36 °C for all 3 IHD Runs. The ultrafilitration (UF) rate and dialysate osmolality were constant throughout the IHD Runs. The most common determinates for UF removal for patients in IHD Run #1 was fluid balance alone,

followed by a combination of fluid balance, chest X-Ray, and patient edema. In IHD Run #2 the three most common determinates of UF removal were a combination of fluid balance and chest X-ray, then fluid balance alone, followed by patient edema. In IHD Run #3, the two most common determinates for UF removal were fluid balance alone and patient edema alone.

Table 2
Intermittent Hemodialysis (IHD) Characteristics

IHD Run # 1			IHD Run # 2			IHD Run # 3		
Characteristic	Frequency	(%)	Characteristic	Frequency	(%)	Characteristic	Frequency	(%)
Length of IHD			**Length of IHD**			**Length of IHD**		
4 hours	3	(27.3)	4 hours	0	(0.0)	4.5 hours	1	(9.1)
5 hours	1	(9.1)	5 hours	3	(27.3)	5 hours	1	(9.1)
6 hours	4	(36.4)	6 hours	5	(45.5)	6 hours	7	(63.6)
7 hours	3	(27.3)	7 hours	3	(27.3)	7 hours	2	(18.2)
Site of Dialysis Catheter			**Site of Dialysis Catheter**			**Site of Dialysis Catheter**		
Subclavian	5	(45.5)	Subclavian	6	(54.5)	Subclavian	7	(63.6)
Femerol	2	(18.2)	Femerol	2	(18.2)	Femerol	2	(18.2)
Internal Jugular	4	(36.4)	Internal Jugular	3	(27.3)	Internal Jugular	2	(18.2)
Anticoagulation			**Anticoagulation**			**Anticoagulation**		
Heparin	5	(45.5)	Heparin	7	(63.6)	Heparin	9	(81.8)
Citrate	6	(54.5)	Citrate	4	(36.4)	Citrate	2	(18.2)
Dialysate Temperature (°C)*			**Dialysate Temperature (°C)***			**Dialysate Temperature (°C)***		
35-35.9	1	(9.1)	35-35.9	1	(9.1)	35-35.9	2	(18.2)
36-36.9	8	(72.7)	36-36.9	4	(36.4)	36-36.9	7	(63.6)
37-37.5	2	(18.2)	37-37.5	6	(54.5)	37-37.5	2	(18.2)

* (°C) = degrees Celsius

Laboratory Values per Intermittent Hemodialysis (IHD) Run

Electrolytes, renal function tests, hemoglobin, hemocrit, and albumin pre and post IHD Runs are outlined in Table 3. The mean sodium pre-dialysis ranged from 136.64 ± 3.44 mmol/L to 137.18 ± 3.37 mmol/L from IHD Run #1 to #3, respectively. The post dialysis sodium was essentially unchanged, with a mean of 136.09 ± 4.30 mmol/L to 137.45 ± 2.58 mmol/L in IHD Run #1 to #3, respectively. The mean potassium pre-dialysis ranged from 4.26 ± 0.65 mmol/L to 4.32 ± 0.89 mmol/L in IHD Run #1 to #3, respectively. In comparison, the post dialysis potassium ranged from 4.03 ± 0.49 mmol/L to 4.23 ± 0.79

mmol/L in IHD Run #1 to #3, respectively. The mean urea pre-dialysis was 26.96 ± 6.58 mmol/L prior to IHD Run #1, compared to a pre-dialysis urea of 19.73 ± 10.88 mmol/L prior to IHD Run #3. The mean post dialysis urea following IHD Run # 1 was 15.80 ± 5.69 mmol/L, compared to 12.83 ± 8.34 mmol/L following IHD Run #3. Pre-dialysis creatinine levels varied with a mean of 332.27 ± 129.76 mmol/L in IHD Run #1 to 293.55 ± 106.84 mmol/L in IHD Run #3. The mean post dialysis creatinine level following the IHD Run #1 was 229.97 ± 62.50 mmol/L, compared to 206.36 ± 70.17 mmol/L after IHD Run #3. The mean pre-dialysis hemoglobin ranged from 80.27 ± 8.76 g/L in IHD Run #1 to 81.64 ± 7.56 g/L in IHD Run #3. The pre-dialysis mean hemocrit levels were 0.23 ± 0.02 l/L in IHD Run #1and remained essentially unchanged in IHD Run #3 at 0.24 ± 0.02 l/L. The post dialysis mean hemocrit levels were similar, with a mean of 0.24 ± 0.02 l/L following IHD Run #1 and a mean of 0.25 ± 0.02 l/L after IHD Run #3. The mean albumin levels pre-dialysis ranged from 25.91 ± 6.53 g/L prior to IHD Run #1 to 25.55 ± 6.77 g/L prior to IHD Run #3.

Table 3
Laboratory Values Pre-Post Intermittent Hemodialysis (IHD) Runs

Pre Intermitteat Hemodialysis (IHD) Run						
	IHD Run # 1		IHD Run # 2		IHD Run # 3	
	Mean ± SD*	Range	Mean ± SD*	Range	Mean ± SD*	Range
Sodium (mmol/L)	136.64 ± 3.44	131-142	136.82 ± 4.89	129-146	137.18 ± 3.37	130-144
Chloride (mmol/L)	99.45 ± 2.62	96-104	99.36 ± 3.17	92-104	100.36 ± 3.47	95-106
Bicarbonate (mmol/L)	24.91 ± 3.04	20-29	26.73 ± 4.62	20-35	25.73 ± 3.82	19-32
Potassium (mmol/L)	4.30 ± 0.68	3.2-5.7	4.32 ± 0.89	2.9-5.7	4.26 ± 0.65	3.5-5.7
Urea (mmol/L)	26.96 ± 6.58	17.1-39.7	22.81 ± 9.50	12.6-43.3	19.73 ± 10.88	6.7-41.3
Creatinine (mmol/L)	332.27 ± 129.76	180-537	313.27 ± 89.80	197-474	293.55 ± 106.84	112-439
Albumin (g/L)	25.91 ± 6.53	16-39	26 ± 5.27	18-34	25.55 ± 6.77	14-34
Hemoglobin (g/L)	80.27 ± 8.76	67-94	83.73 ± 5.85	73-94	81.64 ± 7.56	72-96
Hemocrit (l/L)	0.23 ± 0.24	0.20-0.28	0.24 ± 0.18	0.22-0.28	0.24 ± 0.02	0.21-0.28
Post Intermittent Hemodialysis Run						
Sodium (mmol/L)	136.09 ± 4.30	129-144	136.64 ± 3.55	129-143	137.45 ± 2.58	132-141
Chloride (mmol/L)	99.55 ± 3.14	94-105	99.27 ± 3.60	94-105	101.09 ± 2.91	96-105
Bicarbonate (mmol/L)	26.60 ± 3.29	21-31	27.27 ± 2.79	23-32	26.27 ± 3.46	21-33
Potassium (mmol/L)	4.23 ± 0.79	2.9-3.7	4.03 ± 0.53	3.3-5.0	4.09 ± 0.49	3.2-4.9
Urea (mmol/L)	15.80 ± 5.69	8.2-28.5	14.1 ± 6.27	6.7-30	12.83 ± 8.34	4.5-32.3
Creatinine (mmol/L)	229.27 ± 62.50	168-359	214.91 ± 72.07	112-358	206.36 ± 70.17	112-353
Hemoglobin (g/L)	84.64 ± 10.24	68-99	82.64 ± 6.86	73-96	82.64 ± 9.78	64-95
Hemocrit (l/L)	0.24 ± 0.02	0.20-0.29	0.24 ± 0.02	0.22-0.28	0.24 ± 0.02	0.19-0.29

* SD = standard deviation

Vital Signs, Weight Loss Rate, and Blood Volume per Intermittent Hemodialysis (IHD) Runs

Vital signs of heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and temperature were collected at baseline and every 15 minutes thereafter. Weight loss rate (WLR) and blood volume (BV) from the Integra dialysis machine were also collected. Table 4 outlines these variables pre and post IHD Runs. The mean heart rate ranged from 87.91 ± 16.54 beats per minute (BPM) pre-IHD Run #1 to 81.82 ± 13.71 BPM pre-IHD Run #3. The mean heart rate at completion of the IHD Runs was comparable, with a mean of 90.36 ± 18.09 BPM post IHD Run #1 to 86 ± 14.92 BPM post IHD Run #3. Mean SBP at baseline ranged from a high of 143.73 ± 27.94 mmHg pre-IHD Run # 2 to a low of 133.55 ± 21.80 mmHg pre-IHD Run #3. In comparison, at completion of the IHD Run, the mean SBP was lowest post IHD Run # 2 at 116.55 ± 28.26 mmHg versus post IHD Run #3 now having the highest mean SBP at 130.64 ± 26.12 mmHg. The mean MAP pre-IHD Run #1 of 84.45 ± 14.66 mmHg was comparable to the mean MAP pre-IHD Run #3 at 88.82 ± 11.37 mmHg. The mean MAP post IHD Run #1 was 81.55 ± 17.2 mmHg versus 89.09 ± 19.48 mmHg post IHD Run #3. The pre-WLR and post WLR in IHD Run #1 were essentially the same at 0.77± 0.32 and 0.71 ± 0.37 respectively. IHD Run #3 WLR was also essentially unchanged, with the pre-WLR of 0.76 ± 0.34 and 0.71 ± 0.43 at completion. The mean BV ranged from 0 % pre-IHD Run #1 to -0.47% pre-IHD Run #3. The final mean BV ranged from –5.58% post IHD Run #1 to –8.50% post IHD Run #3 (see Figure 1 and Figure 2).

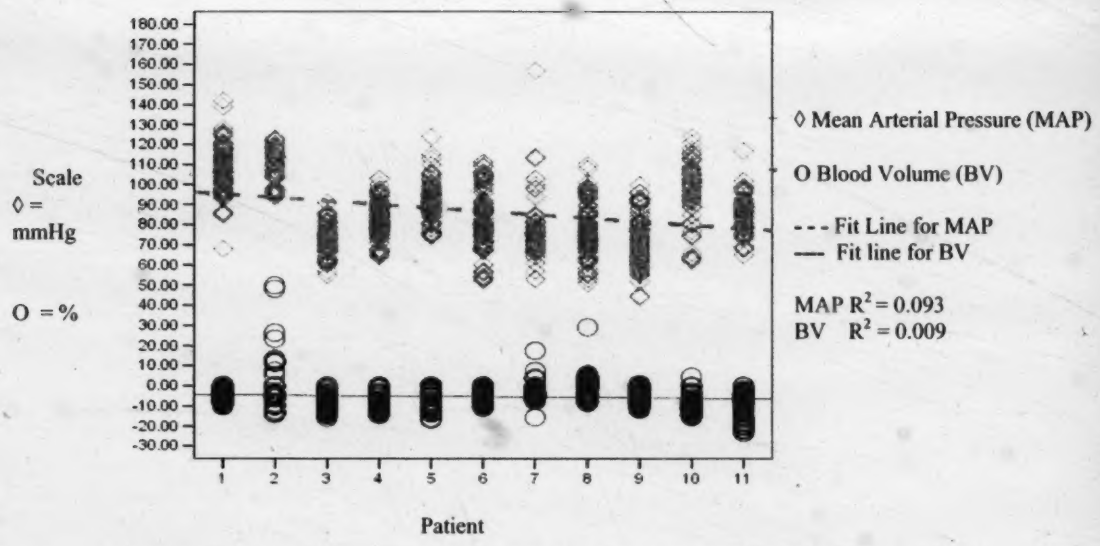

Figure 1. Mean Arterial Pressure (MAP) and Blood Volume (BV) Per Patient

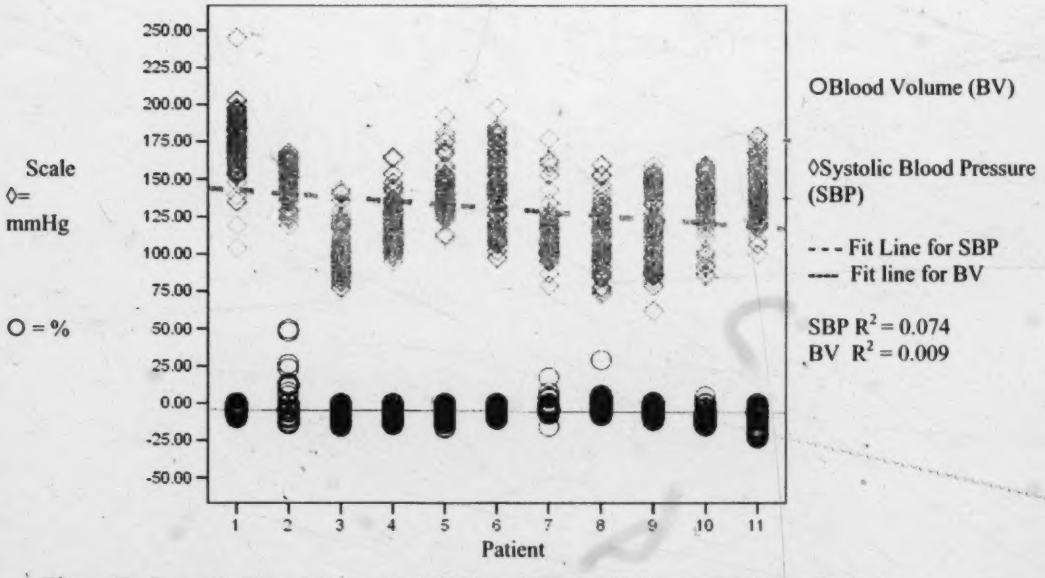

Figure 2. Systolic Blood Pressure (SBP) and Blood Volume (BV) Per Patient

Table 4
Vital Signs during Intermittent Hemodialysis (IHD) Runs

	Baseline Vital Signs					
	IHD Run # 1		IHD Run # 2		IHD Run # 3	
	Mean ± SD*	Range	Mean ± SD*	Range	Mean ± SD*	Range
Heart Rate	87.91 ± 16.54	59-117	91.45 ± 14.86	63-109	81.82 ± 13.71	59-107
SBP*	139.64 ± 23.30	100-175	143.73 ± 27.94	94-178	133.55 ± 21.80	95-171
DBP*	58.73 ± 11.85	39-77	66.36 ± 14.86	40-93	64.64 ± 12.97	49-87
MAP*	84.45 ± 14.66	61-100	91.36 ± 18.22	68-122	88.82 ± 11.37	70-107
Temp. °C*	37.27 ± 0.58	36.2-38.2	37.62 ± 0.81	36-39	37.32 ± 0.47	36.5-38
BV%*	0 ± 0	0 - 0	-0.15 ± 0.51	-1.7-0	-0.47 ± 0.90	-2.9-0
WLR*	0.77 ± 0.32	0.1-1.16	0.59 ± 0.32	.10-1.03	0.76 ± 0.34	.38-1.35
	Final Vital Signs					
Heart Rate	90.36 ± 18.09	57-116	90.64 ± 12.88	60-102	86.00 ± 14.92	63-115
SBP*	122.55 ± 28.01	82-168	116.55 ± 28.36	79-171	130.64 ± 26.12	100-184
DBP*	60.55 ± 15.25	36-83	61.82 ± 18.44	36-95	90.00 ± 16.53	54-98
MAP*	81.55 ± 17.22	55-111	80.55 ± 22.30	53-123	89.09 ± 19.48	72-125
BV%*	-5.58 ± -4.91	-11.7-3.50	-6.76 ± 5.08	-13.4-4.0	-8.50 ± 7.25	-23.3-0
WLR*	0.71 ± 0.37	.10-1.03	0.67 ± 0.31	.33-1.41	0.71 ± 0.43	.10-1.54

* SD = standard deviation, SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, WLR = weight loss rate, BV% = blood volume percentage, Temp. °C = temperature degrees Celsius

Hypotension and Treatment of Hypotension during Intermittent Hemodialysis (IHD) Runs

Hypotension was defined as MAP <70 mmHg or SBP <90 mmHg. Table 5 outlines the frequencies for MAP <70 mmHg, SBP <90 mmHg, and hypotensive episodes. Hypotensive episodes was defined as MAP <70 mmHg or SBP <90 mmHg, however the MAP or SBP had to be >70 mmHg for more than 5 minutes before a new episode could be counted. The frequency of hypotensive episodes in IHD Run # 1 and #3 was 63.6% (n=7) and 81.8% (n=9) in IHD Run #2.

Table 5
Hypotensive Episodes per Intermittent Hemodialysis (IHD) Run

	IHD Run #1		IHD Run #2		IHD Run #3	
	Frequency	(%)	Frequency	(%)	Frequency	(%)
MAP* < 70 mmHg*	7	(63.6)	9	(81.8)	7	(63.6)
SBP* < 90 mmHg*	4	(36.4)	8	(72.7)	3	(27.3)

* MAP = mean arterial pressure, mmHg = millimeters of mercury, SBP = systolic blood pressure

Treatment of hypotension is outlined in Table 6. Although the frequency of hypotension per MAP was high, no treatment occurred in 63.6% (n=7) of the hypotensive episodes in IHD Run #1 and #2, and in 72.7% (n=8) in IHD Run # 3. There were several treatments, with fluid being the most common at 18.2 % (n=2) in IHD Run #1 and #3, and 27.3% (n=3) in IHD Run #2. Treatment with vasopressors occurred in 9.1% (n=1) for IHD Run #1 and #IHD Run #3, and in18.2% (n=2) for IHD Run #2.

Table 6
Treatment of Hypotensive Episodes per Intermittent Hemodialysis (IHD) Run

	IHD Run #1		IHD Run #2		IHD Run #3	
Treatment	Frequency	(%)	Frequency	(%)	Frequency	(%)
No treatment	7	(63.6)	7	(63.6)	8	(72.7)
Fluid	2	(18.2)	3	(27.3)	2	(18.2)
Vasopressors						
Before	1	(9.1)	0	(0.0)	1	(9.1)
During	0	(0.0)	2	(18.2)	1	(9.1)
Increase length of IHD Run	1	(9.1)	0	(0.0)	0	(0.0)
Decrease Weight Loss Rate	1	(9.1)	1	(9.1)	0	(0.0)
Decrease Blood Pump Speed	0	(0.0)	0	(0.0)	1	(9.1)

Blood Volume Slopes

BV slopes are tracings of BV over time during the IHD Run. BV slopes were obtained from a graph generated by continuous BV monitoring on the Integra dialysis machine. The BV slopes can be Flat, Linear Decrease, Concave Upward Increase, Concave Downward Decrease and Indeterminate (Andrulli et al., 2002). The BV slope for each IHD session was classified independently by two raters initially. A Kappa statistic was done for all 3 IHD Runs and is outlined in Table 7. In IHD Run #1, a Kappa statistic of 0.554 was achieved; in IHD Run #2 0.033 and in IHD Run #3 0.542 respectively. The overall percentage agreement between the two raters was 51% (17 out

of 33). Due to the low agreement, a third rater was utilized to classify the BV slopes, with the majority determining the final BV slope classification.

Table 7
Inter-rater Agreement on Classification of Blood Volume Slopes

	IHD Run #1	IHD Run #2	IHD Run #3
Kappa Statistic	0.554	0.033	0.542
p Value	0.001	0.814	0.023

Table 8 outlines the frequency of BV slopes per IHD Run. The most frequent BV slope for all IHD Runs was Linear Decrease at 63.6% (n=7) in IHD Run #1, 45.5% (n=5) in IHD Run #2, and 54.5% (n=6) in IHD Run #3. The next most common BV slope was Concave Upwards Decrease at 9.1% (n=1) in IHD Run #1, and 27.3% in both IHD Run #2 and IHD Run #3. The Flat BV slope occurred for 27.3% in IHD Run #2, and only 9.1% in IHD Run #1 and IHD Run #3, respectively. Concave Downwards Decrease was the least common, occurring only once (9.1%) over the 3 IHD Runs.

Table 8
Frequency of Blood Volume (BV) Slope per Intermittent Hemodialysis (IHD) Run

	IHD Run #1		IHD Run #2		IHD Run #3	
BV Slope	Frequency	(%)	Frequency	(%)	Frequency	(%)
Flat	1	(9.1)	3	(27.3)	1	(9.1)
Linear Decrease	7	(63.6)	5	(45.5)	6	(54.5)
Concave Upwards Decrease	1	(9.1)	3	(27.3)	3	(27.3)
Concave Downwards Decrease	0	(0.0)	0	(0.0)	1	(9.1)
Indeterminate	1	(9.1)	0	(0.0)	0	(0.0)

The frequency of hypotensive episodes per BV slope is outlined in Table 9. In IHD Run #1 Linear Decrease was the most frequent slope at 45% with a total of 16 (69%) hypotensive episodes. However, for IHD Run #2 the frequency of Flat, Linear Decrease, and Concave Upwards Decrease BV slopes was equal at 27.3%. The Flat BV slope had 11 (45%) hypotensive episodes. Linear Decrease had 9 (37%) and Concave Upwards Decrease had 4 (16%) hypotensive episodes, respectively. In IHD Run #3, the most frequent BV slope was Linear Decrease at 45.5% with a total of 8 (66%) hypotensive episodes. Both Flat and Concave Upwards Decrease occurred at 9.1%. The Concave Upwards Decrease slope had 3 (25%) hypotensive episodes with the Flatslope only having 1 (8%) hypotensive episode. There was no significant relationship found between BV slope and hypotensive episodes per IHD Run in this cohort.

Table 9
Frequency of Blood Volume Slopes per Episodes of Hypotension

IHD Run # 1		
Hypotensive Episodes	Slope	Frequency
Less than 5	Linear Decrease	3
	Concave Upwards Decrease	1
Greater than 5	Linear Decrease	2
	Indeterminate	1
IHD Run # 2		
Less than 5	Flat	2
	Linear Decrease	2
	Concave Upwards Decrease	3
Greater than 5	Flat	1
	Linear Decrease	1
IHD Run # 3		
Greater than 5	Flat	1
	Linear Decrease	5
	Concave Upwards Decrease	1

Relationship Between Blood Volume and Blood Pressure

A linear regression was done to determine if there was a relationship between blood volume and blood pressure during IHD Runs (see Figure 3). With the dependent variable as MAP, and the independent variable as BV, there was a correlation of 0.075, accounting for 0.60% of the variance (p=0.70). Another linear regression was done with the dependent variable as SBP, and the independent variable as BV (see Figure 4). There was a correlation of 0.327, accounting for 11% of the variance (p=0.08). Thus, BV did not predict MAP or SBP in this study cohort.

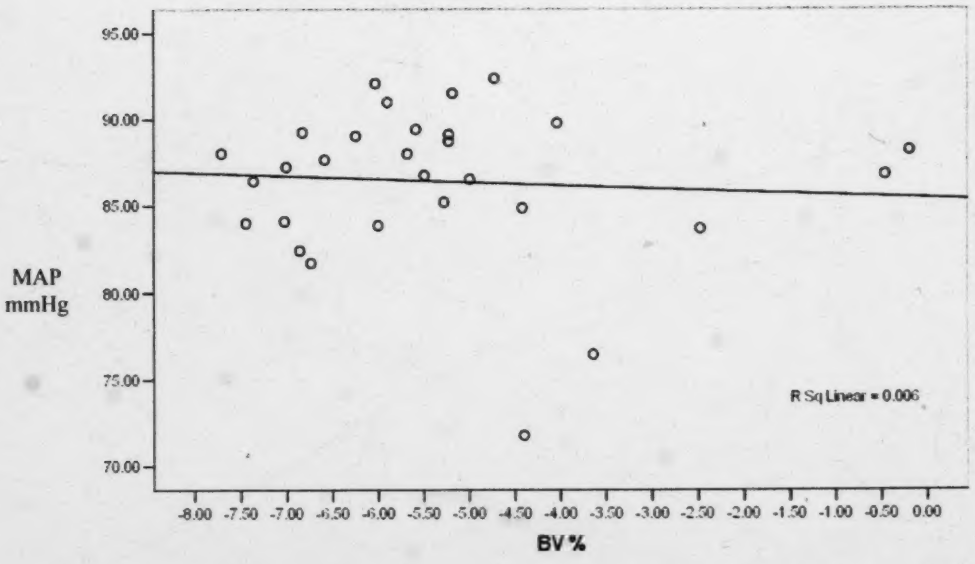

Figure 3. Relationship Between Mean Arterial Pressure (MAP) and Blood Volume (BV)

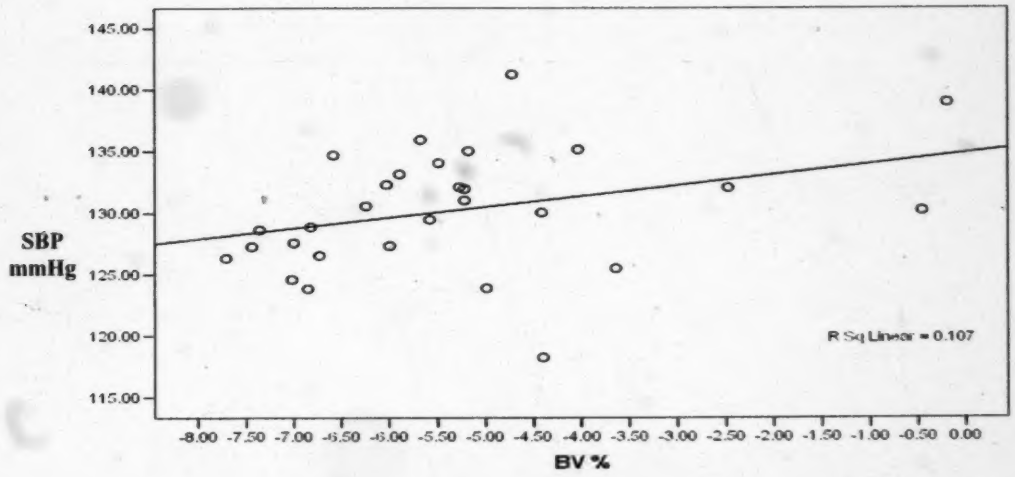

Figure 4. Relationship Between Systolic Blood Pressure (SBP) and Blood Volume (BV)

Critical Blood Volumes

Critical BV is defined as the decrease of BV below a specific value whereby hypotension occurs. To obtain the critical BV, the BV prior to each hypotensive episode during the 3 IHD Runs was averaged to obtain the critical BV for that patient (Begin et al., 2002). Ten patients experienced hypotension, so the CBVs were calculated and are outlined in Table 10. A linear regression was also done to determine the relationship of CBV and blood pressure (see Figure 5). With the dependent variable MAP, and independent variable of BV, there was a correlation of 0.144, accounting for 2.10% of the variance ($p=0.083$). A linear regression was also done with SBP as the dependent variable and independent variable of BV, with a correlation of 0.151, accounting for 2.30% of the variance ($p=0.068$). Thus, a CBV was not determined to be predictive of MAP or SBP (see Figure 6).

Table 10
Critical Blood Volumes for Individual Patients

Patient Number	Critical Blood Volume Mean ± SD*
1	-6.00 ± 0.70
3	-5.23 ± 4.74
4	-4.95 ± 5.25
5	0.00 ± 0.00
6	-5.55 ± 3.54
7	-2.41 ± 5.06
8	1.22 ± 7.48
9	-2.72 ± 2.91
10	-12.8 ± 2.44
11	-16.8 ± 7.38

Note: Patient # 2 does not have a critical blood volume because they never experienced hypotension.

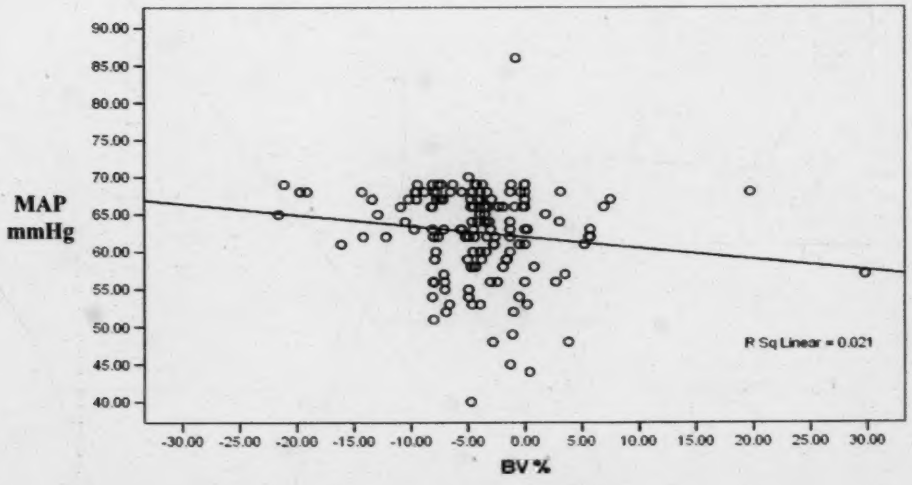

Figure 5. Relationship Between Mean Arterial Pressure (MAP) and Critical Blood Volume (BV)

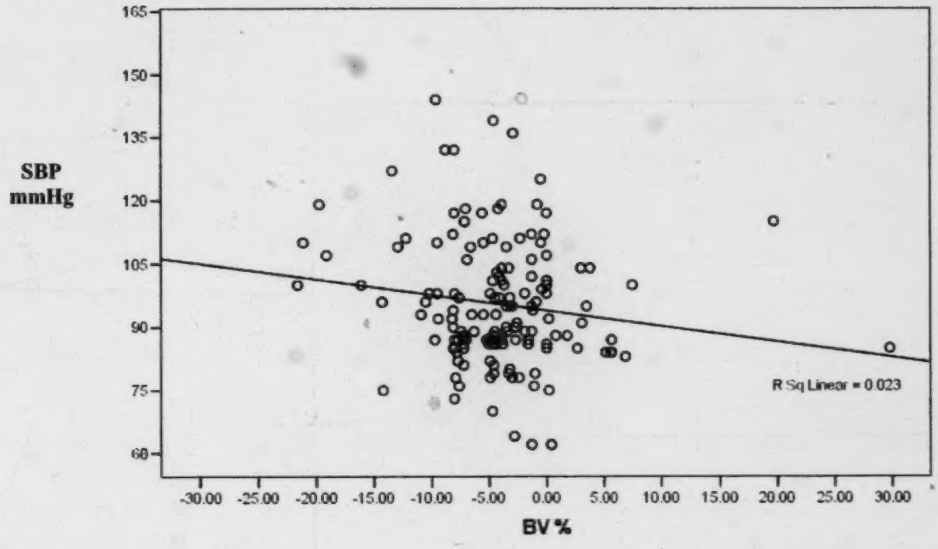

Figure 6. Relationship Between Systolic Blood Pressure (SBP) and Critical Blood Volume (BV)

Chapter Five

Discussion of Findings

A prospective observational design (within subject repeated measures) was used to evaluate the relationship of BV and BV slopes to the development of hypotension in the critically ill acute renal failure (ARF) patient on intermittent hemodialysis (IHD) admitted to the Royal Alexandra Hospital (RAH) General Systems ICU (GSICU). Data were collected on 11 patients, over 3 IHD Runs during the study period of August, 2004 to May 2005. Data analysis included descriptive statistics for subject characteristics and all study variables. Linear regression was done to determine if a relationship existed between BV and MAP or SBP, and Chi-square was done to examine the relationship of BV slopes to hypotensive episodes. Critical Blood Volume (CBV) was determined for each subject by averaging the blood volume prior to episodes of hypotension for the 3 IHD Runs.

Hypotension

Hypotension was defined as a systolic blood pressure (SBP) below 90 mmHg or a decrease of ≥30 mmHg and/or a mean arterial pressure (MAP) below 70 mmHg. The blood pressure had to return to normal for greater than 5 minutes to be considered a new hypotensive episode. Hemodynamically unstable patients who required initiation of vasopressors or titration of vasopressors to maintain a SBP ≥90 mmHg were identified as having a hypotensive episode. Ten of the 11 patients experienced hypotension during hemodialysis. The incidence of hypotension over all 3 IHD Runs according to MAP <70 mmHg was 70%, in comparison to the only other study this incidence is higher than the 30% reported (Tonelli, Astephen, Andreou, Beed, Lundrigan, & Jindal, 2002). The

incidence of hypotension according to SBP <90 mmHg was 45% over all 3 IHD Runs, also higher than the 18% reported by Tonelli et al. This is an interesting finding as the average length of dialysis in this study was longer than most studies, therefore we would have expected the frequency of hypotension to be lower. Studies with IHD Runs >4 hours have shown a decreased frequency of hypotension in ARF patients on dialysis in GSICU (Kumar, Craig, Depner, & Yeun, 2000). It is possible that the small sample size contributed to this finding. Treatment for hypotension is directed by SBP guidelines in the RAH GSICU. Therefore the treatment for hypotension was similar to the frequency of hypotension according to SBP. In IHD Run #1 and IHD Run #2, treatment occurred at 36.4%, respectively. In IHD Run #3 treatment for hypotension occurs 27.3% of the time. The overall percentage of treatment for all 3 IHD Runs was 33%. This is lower than the occurrence for hypotension defined by both SBP < 90 mmHg and MAP < 70 mmHg. There is not a consistent definition for hypotension in either the Chronic Renal Failure or ARF patient. Further research is needed to define the degree of hypotension that affects the recovery of renal failure in the ARF patient.

Blood Volume Slopes

Two raters classified BV slopes for each IHD session independently. The BV slopes could be classified as Flat, Linear Decrease, Concave Upward Increase,and Concave Downward Decrease (Andrulli et al., 2002). A Kappa statistic was completed to assess inter-rater agreement on classification of BV slopes. Inter-rater agreement was moderate to low for all IHD Runs. This may have been due to unfamiliarity of the raters with classification of BV slopes. It would be interesting to see if agreement could be improved by providing education on classification of BV slopes. The most frequent BV

slope was Linear Decrease for all IHD Runs, thus as expected, it was also the most frequent BV slope occurring with hypotension. These findings differ from Andrulli et al.'s (2002), who found Linear Decrease to be the most common only in patients that were normotensive. They found that Concave Upwards Decrease was the most common BV slope in hypotensive patients. This difference may be due to the small sample size of 11 in our study compared to Andrulli et al. (2002) who had a sample size of 123. There was no statistically relevant relationship between BV slope and occurrence of hypotension in our cohort. In view of the low rater agreement and the small sample size it is not surprising that a significant relationship could not be found.

Relationship of Blood Volume to Blood Pressure

BV was obtained at 15 minute intervals, and prior to hypotension, for each IHD Run. BV monitoring devices depend on the fact that the blood components are confined to the vascular space enabling the measurement of relative blood volume. Therefore as plasma water was removed by UF the concentration of the blood compartment increased (HCT) and there was a proportional decrease in circulating BV (Chamney et al., 1999). As expected there was a decrease in BV as ultrafiltration occurred. Although there was a correlation between MAP, SBP, and BV, this relationship was not significant. These finding were similar to Tonelli et al. (2002), who also found monitoring of BV could not predict episodes of forthcoming hypotension.

Several factors may contribute to the inability of BV to predict forthcoming hypotension. Although hypovolemia contributes to hypotension in critically ill patients on IHD there are other contributing factors as well. Other mechanisms such as autonomic dysfunction and abnormal vascular tone may affect plasma refill in the critically ill

patient affecting the ability of BV monitoring to predict hypotension. This study did not measure plasma refill with bioimpedance, which may have clarified whether abnormal vascular tone was contributing to abnormal plasma refill in the critically ill patient. Individual critical blood volume (CBVs) was calculated for all patients that experienced hypotension. However, this study was unable to find a CBV for individual patients that could predict forthcoming hypotension. This may indicate that hypotension is more dependent on cardiovascular defense mechanism such as sympathetic drive rather than on reduction in BV. Thus CBV would not be able to consistently predict forthcoming hypotension, as hypotension if dependent on more than BV.

All patients is this study were dialyzed through central venous catheters. It is believed that blood drawn from these catheters may have different hemocrits affecting the correlation of BV to hypotension differently than when monitored peripherally. Another interesting element that was noted in this study was the high number of interdialytic alarms related to access pressures. This necessitates the blood pump speed be changed which affects the accuracy of BV monitoring. Anytime blood pump speeds are adjusted, BV monitoring needs to be recalibrated and does not start monitoring until the pump speed is > 200 for 5 minutes. This may have affected the reliability of this monitoring device.

Limitations of Study

The small sample size, as well, autocorrelation among multiple data points, may have accounted for an inability to show a statistically significant relationship between BV and hypotension. The physicians and nurses at the RAH GSICU were aware that hypotension in IHD was being evaluated, which could have lead to modification of

treatment of patients on IHD in the GSICU. However, dialytic technique was standardized as much as possible during this study. The length of IHD Runs and Ultrafiltration removal rates varied between patients, however this is the clinical setting that BV monitoring would be used in critical care. In this study both arterial lines and automated sphygmomanometers were used to measure blood pressure, which may have introduced measurement error.

Implications of the Findings

In this study, hypotension was high with an occurrence rate of 70% in critically ill ARF patients on IHD. This is not similar to other studies, which reported hypotension rates of 30% (Tonelli, Astephen, Andreou, Beed, Lundrigan, & Jindal, 2002; Kumar, Craig, Depner, & Yeun, 2000). The detrimental effect of repeated episodes of hypotension on eventual recovery of renal function leads to a desire to find a method of predicting hypotension in these patients. The causes of dialysis induced hypotension include osmolar imbalance (disequilibrium syndrome), inappropriate neurohumoral responses, change in body temperature, and hypovolemia. Understanding of the etiology of hypotension during dialysis may lead to development of optimal dialysis treatment strategies for these patients. In this cohort, the APACHE II scores were higher at 22.73 ± 6.69 than the 20.4 ± 6.0 APACHE II reported by Tonelli et al. (2002). Thus this cohort was slightly more acutely ill which may account for the higher incidence of hypotension.

As well in this cohort there was no significant correlation found between BV and hypotension. There is a subgroup of patients that is described in the literature that experience dialysis-induced hypotension that is not due to hypovolemia but rather to failure of the cardiovascular defense mechanisms. This is described as Type 2

hypotension and is seen in older patient with cardiovascular disease or diabetes (Donauer, Kolbin, Bek, Krause, & Bohler, 2000). Five of the 11 patients in this study had cardiac disease and diabetes mellitus, which may have lead to higher frequency of Type 2 hypotension, BV monitoring has not been shown to be effective at predicting this type of hypotension. Rather, BV monitoring has been moderately successful at predicting hypotension caused by hypovolemia (Type 1 hypotension). This subgroup of patients may benefit from extended daily dialysis with lower ultrafiltration (UF) rates, additional research is required to fully answer this question.

In this study we were unable to show a relationship between BV Slope and hypotension. However the inter-rater reliability for classifying BV slopes was extremely low. BV slopes are described in various manners from study to study and there is no consistent tool to classify these slopes. Development of a standard classification tool for BV Slope may assist researchers to find a relationship between BV slopes and hypotension.

Conclusion

Hypotension occurred in approximately 70% of all IHD Runs of critically ill ARF patients. Monitoring of BV was not shown to predict episodes of forthcoming hypotension in this study cohort. However, this does not preclude the need to implement strategies to reduce hypotension during dialysis. The multifactoral causes of hypotension in ARF patients on IHD indicates that one simple strategy is unlikely to alleviate this problem. A subgroup of critically ill patients cardiovascular defense mechanisms are unable to compensate for reduction in BV in order to prevent hypotension. This subgroup is older, have higher apache scores and have multiple comorbidities such as cardiac

disease and diabetes mellitus. They may benefit from less aggressive dialysis treatment strategies. There is a need for additional research to determine what dialysis treatment would be of the most benefit in preventing hypotension in this subgroup.

In this cohort, all IHD Runs were done via central venous catheters. It has been suggested that difference in hemocrit levels between central blood and peripheral blood compartments affect the correlation of BV to hypotension (Prakash, Reddan, Heidenheim, Kianfar, & Lindsay, 2002; Tonelli et al., 2002). As well, in our cohort there were frequent access alarms which may have affected the reliability of the BV monitoring device. This may have accounted for our inability to determine a relationship between BV monitoring and hypotension in patients dialyzed via central venous catheters. There is a need for further study to determine if a different BV monitoring device designed to use with central venous access could be used to predict hypotension.

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Appendix A

Ultrafiltration Profiles

Profile	Description
UF Profile 0	Constant UF rate during dialysis.
UF Profile 1	Constantly decreasing UF rate during dialysis. UF was started at 1.33 > than the calculated UF
UF Profile 2	Stepwise decreasing UF rate in which every step last 1/3 of the total treatment time. UF rate begins with 1.5 times the calculated UF and decreases to 1 time at 2nd step to 0.5 times 3rd step.
UF Profile 3	Three intervals with a UF rate greater than two times the calculated UF. Interrupted by 3 intervals with UF rates of 100 mls. The duration of the six intervals was equal.
UF Profile 4	Five short intervals with UF rate two times greater than the calculated UF rate. Interrupted by five intervals with a UF rate of 100 mls/hr. The duration of the 10 intervals was equal.
UF Profile 5	Is also divided into 10 intervals. Five intervals of high UF and five intervals of UF rate of 100mls/hr. In contrast to UF profile 4 UF profile 5 begins with 3.2 times the calculated UF and then does a stepwise decrease in the remaining four high UF rate intervals.

(Donauer, Kolbin, Bek, Krause, & Bohler, 2000.)

Appendix B

Capital Health

CARITAS HEALTH GROUP

Hemodialysis Log
Critical Care Program

Date _____ Run # _____ Machine Type / No. _____

Dialyzer _____ Lot No. _____ Time On _____

Dialysis Duration _____ hrs Ultrafiltration _____ hrs Time Off _____

Access: type/site _____ Dialysis set up done by _____

Condition of Access (condition of site, patency of access) _____

Fluid Removal Chart

1. Fluid desired to lose _____ mL
2. Prime / take off addition _____ mL
3. Intake (IV, blood, TF, PO) _____ mL

Total Target Loss _____ mL

Actual Fluid Removed _____ mL

Bath Composition

Na _____ mmol / L

set @ _____ mmol / h

Bicarb / Bicart _____

set @ _____ mS / cm

K _____ mmol / L

Other _____

Profiling

UFR (WLR) ☐ Variable ☐ Linear

Na (Cond) x Hours

_____ x _____

_____ x _____

_____ x _____

_____ x _____

Anticoagulation

☐ Heparin ☐ Citrate ☐ Other

Concentration _____

Initial Bolus _____ Rate _____

Heparin Free Dialysis NS flush q ____ h

Dialysis Mode Initiated _____ hrs.

Dialysis Safety Checks

Conductivity measured / machine _____

pH measured / machine _____

Sterilant (Bleach, Amuchina) Clearance: Start of Run ☐ Negative

End of Run ☐ Negative

Vital Signs Section

Time	BP	Pulse	Press A / APS	Press V	TMP	TWL / WLR	Anticoagulation ☐ Heparin (mL) ☐ Citrate (mL) ACT / Ca^{++}	Hourly rate / Bolus (mL)	Pump Speed	BV % / Diascan	Comments	Init

Hemodialysis Complication

1. None			6. Cardiac Arrest			11. Convulsion			Init	Signature	
2. Blood Reaction			7. Hypertension			12. Collid Admin					
3. Clotted Artificial Kidney			8. Arrhythmia			13. Fever-Chills					
4. Hypotension SBP < 85 mmHg			9. Vasopressor			14. Artifical Kidney Rupture					
5. Drug Reaction			10. Bleeding			15. Mechan. Problem					
16. OTHER (Describe):											

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Appendix B

Capital Health

CARITAS HEALTH GROUP

Hemodialysis Log
Critical Care Program – Continued

Date _____ Run # _____

Anticoagulation
☐ Heparin (mL)
☐ Citrate (mL)

Vital Signs Section

Time	BP	Pulse	Press A / APS	Press V	TMP	TWL/ WLR	ACT / Ca^{++}	Hourly Rate / Bolus (mL)	Pump Speed	BV % / Diascan	Comments	Init

Appendix C

Data Collection Sheet

Patient Study #_____ IHD Session #_____

Demographic Variables:

Age: _____ Gender: ☐ Male ☐ Female. BMI: _____ APACHE II Score: _____

Diagnosis: _____

Comorbities:

_____

Medications:

_____

_____

Previous dialysis treatment: ☐ Yes ☐ No

Baseline laboratory data (morning routine bloodwork):

Sodium: _____ Chloride: _____ Bicarbonate: _____ Potassium: _____

Urea: _____ Creatinine: _____Albumin: _____ Hgb: _____HCT: _____

Temperature: _____

Postdialysis (6 hours after IHD session):

Sodium: _____ Chloride: _____ Bicarbonate: _____ Potassium: _____

Urea: _____ Creatinine: _____ Hgb: _____HCT: _____

Vasopressors: ☐ Yes ☐ No

If yes indicate if on vasopressors prior to initiation of dialysis, or if initiated during dialysis and any changes during dialysis: _____

BV slope:

Classified as:_____ by researcher.

Classified as:_____ by intensivist

Appendix D

Study Procedure:

We will collect the following health information such as age, gender, reason for admission to the GSICU, Apache II score (a point based score to assess severity of disease), other medical history, heart rate, blood pressure and blood volume values from your hospital chart.

Risks:

There will be no adverse effects or risks associated with participating in this study. Only information documented on your hospital chart will be obtained. If you decide not to participate in this study, you will receive the standard medical/nursing care that is normally given for acute renal failure, which includes, IHD, drawing of blood work as deemed clinical necessary by your physician.

Benefits:

There is no direct medical benefit from taking part in this study, although the results of this study may in the future benefit other patients with acute renal failure.

Voluntary Participation:

If you decide not to take part in this study you will receive the standard medical/nursing care that you would normally receive as a patient with acute renal failure. If you change your mind after you have agreed to take part in the study, you can stop the study at any time by contacting the investigator without affecting your care.

Appendix E

Determination of UF Volume

To be completed by the Intensivist or designate. Please indicate which of the following parameter were utilized to determine UF volume removal for this patient.

- ☐ Daily fluid balances.
- ☐ Chest X-ray appearance
- ☐ Estimation of edema (JVD or pitting edema)
- ☐ CVP or PCWP
- ☐ Kt/vf
- ☐ Urea and creatinine levels
- ☐ Pre-dialysis weight